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Ben-Sahra et al. Cancer & Metabolism 2014, 2(Suppl 1):P6
http://www.cancerandmetabolism.com/content/2/S1/P6

Cancer & Metabolism

POSTER PRESENTATION Open Access

mTORC1 stimulates nucleotide synthesis through both transcriptional and post-translational mechanisms

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From Metabolism, Diet and Disease 2014: Cancer and metabolism
Washington DC, USA. 28-30 May 2014

Background

Cellular growth signals stimulate anabolic processes. The mechanistic target of rapamycin (mTOR), as part of mTORC1, is a protein kinase that senses growth signals to regulate anabolic growth and proliferation. mTORC1 stimulates protein synthesis through effects on mRNA translation and ribosome biogenesis [1]. mTORC1 signaling also promotes *de novo* lipid and sterol synthesis through the activation of the sterol-response element-binding protein (SREBP) transcription factors, which stimulate the expression of the enzymes driving this biosynthetic process [2].

Material and Methods

TSC2 $^{+/+}$ MEFs, *TSC2* $^{-/-}$ MEFs, MCF10A expressing pBabe-empty vector or PI3KCA^{H1047R}, HeLa cells, U87MG cell line were used in this study. To determine the relative levels of intracellular metabolites, extracts were prepared and analyzed by LC/MS/MS [3]. Regarding the U-^{14}C-aspartate, U-14C-glycine incorporation into RNA and DNA, cells were serum starved for 15 hours and treated as indicated. Cells were harvested and RNA or DNA was isolated using Allprep DNA/RNA kits according to the manufacturer's instructions and quantified using a spectrophotometer. For statistical analysis a two-tailed Student's t-test was performed for all pairwise comparisons (n=3).

Results

We find that activation of mTORC1 leads to the acute stimulation of metabolic flux through the *de novo* pyrimidine synthesis pathway [4]. We recently found that mTORC1 stimulates the *de novo* purine synthesis pathway. In contrast with pyrimidine synthesis, the regulation of the purine synthesis by mTORC1 signaling occurs through long-term mechanism. Indeed, we found that mTORC1 regulates the *de novo* purine synthesis pathway through the transcription factor SREBP.

Conclusion

These findings demonstrate that growth signaling through mTORC1 promotes the production of new nucleotides to facilitate an increased demand for RNA and DNA. mTOR appears to be a central regulator of *de novo* nucleotide synthesis. Therefore, nucleotide synthesis joins protein and lipid synthesis as major anabolic processes stimulated by mTORC1 signaling.

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Published: 28 May 2014

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doi:10.1186/2049-3002-2-S1-P6
Cite this article as: Ben-Sahra *et al.*: mTORC1 stimulates nucleotide synthesis through both transcriptional and post-translational mechanisms. *Cancer & Metabolism* 2014 **2**(Suppl 1):P6.

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